

REMARKSStatus of the Claims

Claims 1-14 are pending in this application. No claims have been canceled or added. Claim 4 has been amended to correctly recite the last member of the Markush group and insert a parenthesis. No new matter has been added by the above claim amendments.

Rejection under 35 USC 112, second paragraph

The Examiner rejects claim 4 as indefinite because of a missing parenthesis. Applicants amend claim 4 to insert the missing parenthesis. As such, the rejection should be withdrawn.

Rejections under 35 USC 103(a)

The Examiner rejects claims 1-14 as obvious over USP 6,368,629 to Watanabe et al. (Watanabe '629) in view of EPO 0284039 to Lida (EP '039). Applicants traverse the rejection and respectfully request the withdrawal thereof.

Watanabe '629 discloses a system for releasing a drug in the colon of the gastrointestinal tract. The drug is coated with an organic-acid-soluble macromolecular substance and a saccharide, which rapidly generates an organic acid when in contact with enteric bacteria in the lower gastrointestinal tract and releases the drug specifically in the colon of the gastrointestinal tract (See column 4, lines 46-54).

Basically, the specific saccharides, such as lactulose are disintegrated by enteric bacteria, which rapidly generates an organic acid. This allows for the macromolecular substance to dissolve and the drug is released specifically in the colon (See col. 3, lines 63 to col. 4, line 7). The saccharide is an essential ingredient in the invention disclosed in Watanabe '629.

On the other hand, no saccharide is required by the present invention.

EP '039 discloses a slow-release pharmaceutical composition which comprises at least one kind of molecule selected from a group of adenine, cystine and tyrosine (See p.2, line 52 to p.3, line 3). The referenced invention of EP '039 only discloses a slow-release pharmaceutical composition to maintain effective levels of the drug in the blood for a prolonged period of time. EP '039 does not disclose or suggest a slow release drug that releases the drug selectively in the lower gastrointestinal tract as in the present invention.

Although EP '039 discloses a group of adenine, cystine and tyrosine, Applicants submit that there is no motivation for one of ordinary skill in the art to chose cystine from the group of adenine, cystine and tyrosine to be used with Watanabe to arrive at the present invention, particularly since neither adenine and tyrosine has disulfide bonds, and thus are not relevant to the present invention.

Although, Example 9 of EP '039 discloses a slow release tablet which contains L-cystine. This particular tablet is likely not to be dissolved to release the drug in the lower gastrointestinal tract as in the present invention at the same rate because the dissolution profile in solution is at pH 6.8. The performance over 8 hours of the slow release tablet in Figure 8 in EP '039 demonstrates that the tablet does not have similar properties as compared to the present invention and to the composition in Watanabe '629.

Neither Watanabe '629 nor EP '039 suggests the interaction between a compound having a disulfide bond and a polymer, as with the polymer (B) in the present invention. The present invention recognizes the rapid release of a drug selectively in the lower gastrointestinal tract, by means of compound (A) having a disulfide bond, such as cystine. The presence of the disulfide bond allows for the compound to be disintegrated into smaller molecules by breaking the disulfide bonds with the reductive action by enterobacteria, which in turn allows for the smaller molecules to have improved solubility in water and/or stronger acidity as compared to the compound (A). See page 14, line 21 to page 15, line 19 of the present specification.

As described in Test 1 (Figs. 1-4) and Test 3 (Fig. 6) in the present specification, in a *simulated* environment in the small intestine at pH 6.8 as in Example 9 in EP '036 by Iida et al., the present invention does not disintergrate; however, the

tablet of EP '039 does disintergrate at a pH 6.8. Moreover, as described in Test 2 (Fig. 5), when a drug was actually administered to a small animal, the release of the drug was controlled even after the enteric film disappeared. The selective release of the drug was performed within the time period of about two hours in the cecum or in the colon.

In light of the above arguments, Applicants submit that one of ordinary skill in the art would not be motivated to combine the teachings in Watanabe '629 and EP '039 to arrive at the present invention. As such, no prima facie case of obviousness has been established and the rejection should be withdrawn.

The Examiner also rejects claims 1-14 as obvious over USP 6,004,583 to Plate et al. Applicants traverse the rejection and respectfully request the withdrawal thereof.

Plate '583 discloses a therapeutic-containing composition adapted for oral administration, which comprises a water insoluble but water swellable polymer chemically modified with a chemical agent, which reduces the degradation or deactivation of the therapeutics. Dimethylaminoalkyl methacrylate or chitosan are discloses as examples of these polymers. (See col.7, line 36 to col.9, line 15).

In Plate '538 at col. 18, lines 4-28, in the explanation of the reaction for introducing a functional group onto the surface of a protease inhibitor, such as ovomucoid, a cystine or a thiol group in a protein as a functional group of chemical reaction,

Plate '538 fails to disclose that a cystine is added as a component of the composition for the value of the disulfide bonds.

In Plate '538, the original content of the composition is not enteric as in the present invention. In the present invention "it is, therefore, more convenient and preferred to administer the therapeutic containing composition of this invention in tablet form or gel capsules as is well known to the art. When administered in that form then the tablet or gel capsule is enterically coated." (See col. 20, line 3-7). Moreover, in Plate '538, the original therapeutic composition is not dissolved site-specifically in the gastrointestinal tract.

Plate '538 also fails to disclose specific disintegration in the lower gastrointestinal tract, as this is not the objective of Plate '538. Plate '538 also fails to disclose a composition of cystine and chitosan.

In Plate '538, it is mentioned that a polymer may also contain a chemical functionality (e.g. cystine) which has an interactive affinity for target receptors located on the transport barrier walls of the digestive tract of the intended human or animal species. However, Plate '538 does not teach a component like polymer (A) of the present invention, which has the property of being decomposed by enterobacteria.

For the forgoing reasons, Applicants submit that Plate '538 fails to disclose or suggest all of the elements of the present

invention. Thus, no prima facie case of obviousness has been established and the rejection should be withdrawn.

Conclusion

As Applicants have addressed and overcome all rejections in the Office Action, Applicants respectfully request that the rejections be withdrawn and that the claims be allowed.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of \$930.00 is attached hereto.


Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kecia Reynolds (Reg. No. 47,021) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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